HUMAN GENETICS

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THE early attempt of the biometricians under Karl Pearson to establish human heredity as a quantitative science ended in failure. In the years which followed, a vast amount of information on heredity in man was published all over the world. Much of it was collected rather uncritically and without a proper understanding of the requirements of a scientific inquiry and is of little more than anecdotal value. But during the past decade or two, human genetics has once more started to emerge as a unified branch of science on new fundamental bases. First and foremost among these is the realization that human genetics is essentially the genetics of a natural population. This shifts the interest from the individual pedigree to the population as a whole and leads to the collection of data which can be interpreted in terms of population dynamics. Next comes the necessity of a critical re-assessment of human data in the light of concepts established by experimental genetics such as multiple allelomorphism, mimic genes, modifiers, etc., and the attempt to construct linkage maps of human chromosomes. Finally, while inherited congenital abnormalities are difficult to study in man, the numerous metabolic and degenerative disorders of post-natal life offer excellent material for physiological genetics, and in this field, at least, human genetics can make its own contribution to genetics as a whole rather than appear in the role of a beneficiary. The progress made by human genetics in these various directions is very uneven, and the egg-shells of the anecdotal phase still stick to it in all too many places. To sift the enormous literature on the subject which covers the whole range of medicine ; to separate the grain from the chaff ; to re-assemble and to re-assess the data within the framework of a unified scientific theory of human genetics ; ulti-mately to present a readable account of this vast field of inquiry—this would appear to be the aim in writing a modern and comprehensive book on the subject. It is a Herculean task indeed, and no reasonable reader would expect any single author to be able to solve this problem with equal mastery throughout. It is with this in mind that the critical remarks on Professor Ruggles Gates's new work* should be understood.

The scope of the book may best be gauged from the headings of the thirty-one chapters into which the work is divided. They are : Introduction ; General Principles of Heredity in Man ; Human Cytology ; Linkage ; Eye Color and Hair Color ; The Inheritance of Color-Blindness ; Hereditary Variations and Abnormalities of the Eye ; Hereditary Variations and Abnormalities of the Ear ; Albinism ; Abnormalities and Diseases of the Skin, Hair, Nails and Teeth ; Anatomical Abnormalities of the Hands, Feet and Limbs ; Abnormalities of the Skeleton and of Bone Structure ; Metabolic Defects and Derangements ; Hæmophilia and Related Hereditary Conditions ; Other Inherited Diseases and Abnormalities of the Blood System ; The Blood Groups—Genetical and Racial Aspects ; Allergy ; Hereditary Syndromes ; Inherited Abnormalities of the Alimentary Canal and Adnexa ; Inheritance of Various Sexual and Intersexual Conditions ; Twins and Twinning ; Inherited Muscular and Neuromuscular Abnormalities ; Hereditary Variations, Defects and Diseases of the Nervous System ; The Inheritance of Mental Defects ; The Inheritance of Normal Mental Differences ; Cancer, the Genetic Aspects ; Constitution, Body-Build and Susceptibility ; Congenital Anomalies ; Inheritance of Stature and Size ; Anthropological Characters ; Odds and Ends.

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* Gates, R. R., *Human Genetics*, New York, 1946. The Macmillan Company. 2 vols. Pp. xvi + 1518. Price 75s.

Throughout the book there are numerous references to related conditions in various animals which will be welcome to medical readers. Each chapter is followed by an extensive bibliography; a rough estimate of the total number of references leads to the somewhat staggering figure of 5,500, and for this large classified list of titles alone, Ruggles Gates's work will be of great value to geneticists and medical men alike. The book is supplemented by a carefully prepared index of 89 pages.

A book of this dimension is unavoidably based on thousands of notes and abstracts of papers collected over a considerable period of time. The editing of this raw material when writing the various chapters unfortunately leaves much to be desired. Very often, related matters in the same chapter are separated by long passages or pages referring to other subjects, and not very rarely the same paper is summarized twice over in the same chapter. The second half of p. 442 occurs again verbatim on pp. 508-509. As a consequence of these editorial shortcomings, many sections do not give the impression of an organic whole, but of a succession of more or less unconnected notes which have not been sufficiently integrated when the chapter was prepared for the press. Though this makes for a somewhat jolting progress and requires a good deal of extra attention when reading, it is perhaps not easily avoided altogether in a work of this magnitude.

As the author points out in the preface, the approach has been biological rather than more strictly genetical throughout. As a consequence the treatment of data tends to be qualitative rather than quantitative and little attempt has been made at a critical statistical evaluation of the raw material. Though this may be welcomed by some medical readers, it will be regretted by geneticists. However, the delimitation and approach to his field is for the author to decide, and it should not be held against him if the reader does not find in his book what he had hoped to find.

Criticism is, however, legitimate within the confines of the author's chosen field, and in what follows, attention is drawn to certain of Professor Gates's tenets in the field of genetics which may mislead the non-genetical reader and in particular the medical man who is apt to accept this book as an authoritative text in matters genetical.

In the field of cytology, Professor Gates maintains that man and indeed the primates in general are tetraploid species. This is deduced from the fact that among the marsupials the commonest chromosome number is 22 or just under one half of that in most primates (48), and that in the nuclei of normal human tissues four nucleoli are found. The entire lack of evidence for the existence of polyploidy in bisexual animals and the serious theoretical grounds against such a hypothesis are brushed aside by a reference to certain diœcious plants (*Melandrium, Salix*) in which polyploidy has been established without a serious upset of the sex-determining mechanism, examples which are not strictly relevant to the argument. The non-genetical reader should realize that this tetraploid interpretation of human cytology is not shared by the overwhelming majority of competent cytologists and is almost certainly an erroneous conception.

In the field of genetics proper, only a few of Professor Gates's heterodox opinions can be discussed here. He is impressed by the fact that many conditions are known in man which are caused either by an autosomal dominant, or by an autosomal recessive, or by a sex-linked recessive gene. To account for this common observation, he advances the hypothesis that such triple genes are in reality only changes in a single locus. As far as the autosomal dominant and recessive are concerned they may be allelomorphic to each other. The sex-linked variety of " the " gene is regarded as due to a translocation of the autosomal dominant gene on to the X-chromosome. But, as most sex-linked genes known are recessives, the further (admittedly purely hypothetical) assumption is made that a change of dominance has taken place as a result of a position effect ! Let us suppose for the moment that this hypothesis were true. Then the gene in question would occur twice

in the chromosome complement, once in an autosome and once (by translocation) in the X-chromosome. Then a recessive mutation happening in the autosomal gene would not manifest itself because of the normal allele carried in the X-chromosome, and a recessive mutation occurring in the sex-linked gene would similarly be " covered " by the autosomal gene. Hence Professor Gates's ingenious hypothesis does not even account for the observed facts, at least not without making further *ad hoc* assumptions. Furthermore, spontaneous translocations are extremely rare and very unlikely to establish themselves in an animal population. That this should have happened not once, but scores of times and hence involving numerous different autosomes is too far-fetched a supposition to be seriously entertained.

Actually, genes with similar effects (" mimic") genes) are not peculiar to man ; many examples are known in *Drosophila* where there is certainly no evidence whatsoever for such an explanation of " mimics." In mammals a very striking example occurs in the mouse, though in this case autosomes only are involved. There are seven recessive genes, each occupying a different autosome, which produce circling movements, head-shaking and deafness and which are almost indistinguishable from each other clinically ; they are waltzing, shaker-1, shaker-2, jerker, Kreisler, pirouette and dervish. In addition there are some six other genes which produce the same syndrome along with complications elsewhere in the body. The pathological analysis is not yet complete, but it is clear that in some of these cases the same clinical syndrome is produced by very different pathological processes ; in other cases the syndrome is produced by similar pathological processes. Such " mimics " probably find their explanation by the fact that if a succession of processes $a \to b \to c \to d \to e$ happening in series is interrupted anywhere along its length, the final result will always be a disturbance of the end product *e*. Models of this type of mechanism have been discovered in recent years in the biochemical mutants of the bread-mould *Neurospora*.

There is thus no need for the speculations advanced by Professor Gates to explain the mimic genes in man.

On p. 83 the author gives a list of " probable or possible autosomal linkages." Of the 48 cases enumerated, 24 are given without qualification, 8 as " probable," 13 as " possible," one case " may be one gene " and two cases are given as " ?." On closer inspection this impressive list contains numerous instances which almost certainly are simply the pleiotropic effects of single genes—for instance absence of macula and aniridia, retinitis pigmentosa and deafness, retinitis pigmentosa and glaucoma (" possible "), aniridia and syndactyly (" possible "), opalescent dentine and lamellar cataract and fits (" possible "), defective enamel and juvenile cataract (" possible "), camptodactyly with (1) anonychia pollicum, (2) absence of patella, (3) luxation of head of radius, myoclonus and epilepsy (" possible "), and tylosis palmarum and plantarum and lipomata, to give only a few representative examples.

How has this misconception arisen ? The answer is perhaps best illustrated by a further (" probable ") case involving apical dystrophy and macular coloboma which was originally described by Sorsby.[*] The syndrome occurred in a mother and five of her seven children ; the mother's parents and her ten sibs were all normal. We read (p. 191) :

> " Probably two linked genes are involved, the apical dystrophy being of the type described by MacArthur and McCullough. It appears probable (*sic* !) that the eye defect and the skeletal defect were separate mutations, arising together in the same chromosome in one of the germ cells that produced the mother. If in homologous chromosomes, they would not be linked in the offspring. The alternative is one mutation with multiple effects."

To take an incidental error first, if the postulated two genes had arisen in homologous chromosomes, they would of course still be linked, but they would be in the repulsion phase. The main argument here as elsewhere is that there are pedigrees with

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[*] *Brit. J. Ophthalm.*, 1935, 19, 65-90.

condition A alone, and pedigrees with condition B alone. Hence, Professor Gates argues, if we find a pedigree with A + B the two genes must be linked. Let us suppose for a moment that in this and all the similar instances quoted by Professor Gates we were really dealing with cases of linkage. We should then have to assume that all these pedigrees show the two postulated genes in the coupling phase. But in a population at equilibrium the coupling and repulsion phase should be equally frequent. Hence we should expect a similar number of pedigrees with the two postulated genes in the repulsion phase. Their complete absence alone is sufficient proof that Professor Gates's linkage hypothesis is untenable. The true explanation is, of course, that which Professor Gates in this particular case quotes diffidently as an alternative explanation, namely one gene with effects A + B.

There are many cases in experimental genetics where non-allelic genes with the three phenotypes A, B and A + B occur. For instance, as mentioned above, there are several genes in the mouse with circling movements, head-shaking and deafness. Also, there are several genes which shorten the tail. That the gene for shaker-short which combines these features should be regarded as a case of linkage of a shaker gene with a short-tail gene would scarcely have occurred to an experimental geneticist.

In addition, there are instances where single and combination phenotypes occur within the same series of multiple allelomorphs. In the mouse, for instance, there occurs the series light-bellied agouti, dark-bellied agouti, light-bellied non-agouti and dark-bellied non-agouti. In this case the hypothesis of two extremely closely linked genes has indeed been ventilated though the two suspected genes have never been separated by an observed crossing-over. That the two-gene hypothesis is almost

certainly incorrect follows from a recent observation[*] which can be explained as a single mutation on the multiple allele hypothesis, but requires the very unlikely assumption of two simultaneous mutations on the alternative hypothesis. It will be remarked that the latter is precisely the interpretation which Professor Gates puts on the case under discussion, and that apparently without any qualms.

Limitations of space, already unduly strained, make a full discussion of many other points impossible. These include sex-linked inheritance, where crossing-over between X and Y-chromosome is assumed all too freely ; inheritance in the Y-chromosome which is postulated in several cases where alternative explanations, such as sex-limitation, are far more likely, and attached X-chromosomes which are several times introduced on insufficient evidence.

Professor Gates's work is likely to be widely used on account of the large field covered and of the extensive bibliographies which make it an invaluable work of reference. In so far as the readers are geneticists, the heterodox views discussed above and others not mentioned will be of little consequence. But the work will also undoubtedly be used by medical men without critical judgment in the field of genetics. As such readers will not be inclined to question the validity of the genetical discussions, the critical remarks made above were considered necessary. The reviewer has done so with some reluctance ; being himself the author of a much smaller monograph, he is full of admiration for the bee-like industry with which Professor Gates has tackled single-handed a field whose vastness might have frightened many a syndicate of authors.

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[*] Little, C. C., and Hummel, K. P. (1947), *Proc. Nat. Acad. Sci.*, 33, 42-43.